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(54) Method of treating alopecia.

(57) The present invention relates to the use, for the manufacture of a medicament to be employed in the prevention or treatment of alopecia, of tellurium compounds or pharmaceutically acceptable salts and complexes thereof.

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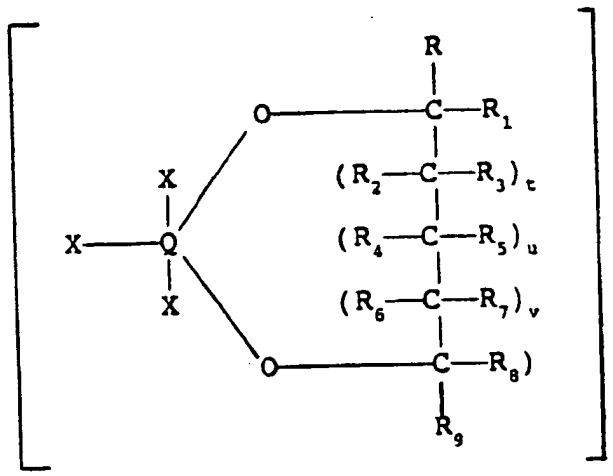
Alopecia which is the partial or complete loss of hair may result from genetic factors, aging, antineoplastic chemotherapy or other causes. Noncicatricial alopecia occurs without scarring or gross atrophic changes. These types of alopecia include male pattern baldness, toxic alopecia, alopecia areata and trichotillomania. In recent years toxic alopecia which is by antineoplastic chemotherapy has become a more common problem as the use of chemotherapy for neoplastic diseases has expanded. This is one of the toxic effects that is seen frequently with alkylating agents, anti-metabolites, plant alkaloids, anti-tumor antibiotics and interferons is alopecia. This problem is particularly distressing to patients who are recovering from chemotherapy because it persists being after any period of hospitalization is required and causes many patients deep psychological difficulties.

Male pattern baldness and other types of alopecia have been resistant to treatment and at the present time, minoxidil is the only recognized therapy for male pattern baldness.

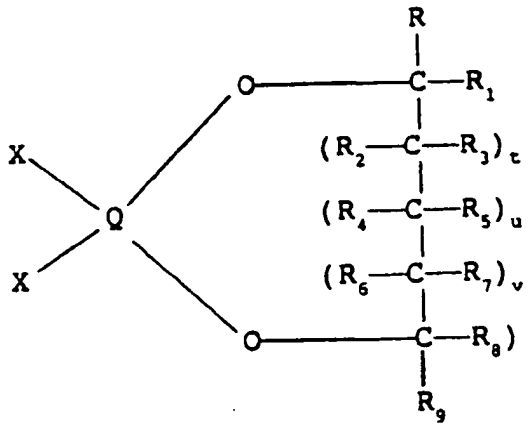
A composition obtained from the bacteria Serratia marcescens has been used to protect against the alopecia which is associated with the use of cytosine arabinoside and doxorubicin. This composition had no effect on alopecia which was induced by cyclophosphamide.

The applicants have discovered that noncicatricial or nonscarring alopecia including the alopecia associated with the therapeutic doses of antineoplastic agents may be avoided or reduced by the prior concomitant or subsequent administration of an effective amount of an effective tellurium compound. The invention therefore proposes the use, for the manufacture of a medicament to be employed in the prevention or treatment of alopecia, of a compound, which is:



(A)

or



(B)

or

TeO_2 or complexes of TeO_2 (C)

or

$PhTeCl_3$ (D)

or

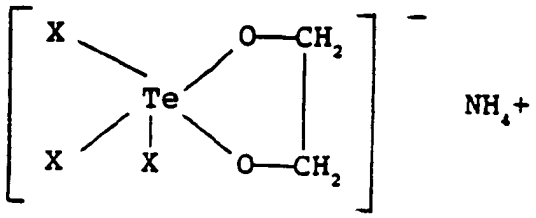
$(C_6H_5)_4\ P^+(TeCl_3(O_2C_2H_4))^-$ (E)

or

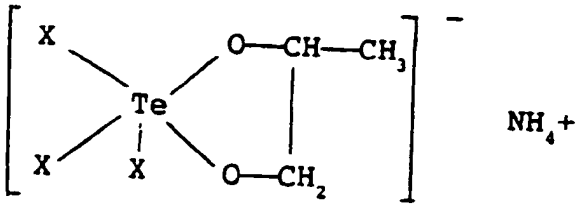
TeX_4, (F)

wherein Q is Te or Se; t is 1 or 0; u is 1 or 0; v is 1 or 0; R, R_1, R_2, R3, R_4, R_5, R_6, R_7, R_8, and R_9 are the same or different and are independently selected from hydrogen, hydroxyalkyl of 1 to 5 carbon atoms, hydroxy, alkyl of 1 to 5 carbon atoms, halogen, haloalkyl of 1 to 5 carbon atoms, carboxy, alkylcarbonylalkyl of 2 to 10 carbon atoms, alkanoyloxy of 1 to 5 carbon atoms, carboxyalkyl of 1 to 5 carbons atoms, acyl, amido, cyano, amidoalkyl of 1 to 5 carbon atoms, N-monoalkylamidoalkyl of 2 to 10 carbon atoms, N,N-dialkylamidoalkyl of 4 to 10 carbon atoms, cyanoalkyl of 1 to 5 carbon atoms alkoxy of 1 to 5 carbon atoms, alkoxyalkyl of 2 to 10 carbon atoms and $-COR_{10}$ wherein R_{10} is alkyl of from 1 to 5 carbon atoms; Y is a cation and X is halogen;
or pharmaceutically acceptable salts and complexes thereof.
The preferred pharmaceuticals acceptable salts are those wherein Y is ammonium or potassium. The compounds with the five membered rings are preferred.

As used herein and in the appended claims, the term alkyl of 1 to 5 carbon atoms includes straight and branched chain alkyl groups such as methyl; ethyl; n-propyl and n-butyl; the term hydroxyalkyl of 1 to 5 carbon atoms includes hydroxymethyl; hydroxyethyl; hydroxy-n-butyl; the term halkoakyl of 1 to 5 carbon atoms includes chloromethyl; 2-iodoethyl; 4-bromo-n-butyl; iodoethyl and 4-bromo-n-pentyl; the term alkanoyloxy of 1 to 5 carbon atoms includes acetyl, propionyl and butanoyl; the term carboxyalkyl includes carboxymethyl, carboxyethyl and ethylenecarboxy; the term alkylcarbonylalkyl includes methanoylmethyl and ethanoylethyl; the term amidoalkyl includes $-CH_2CONH_2$; $-CH_2CH_2CONH_2$ and $-CH_2CH_2CH_2CONH_2$; the term cyanoalkyl includes $-CH_2CN$; $-CH_2CH_2CN$ and $-CH_2CH_2CH_2CN$; the alkoxy, of 1 to 5 carbon atoms includes methoxy, ethoxy, n-propoxy and n-pentoxy; the terms halo and halogen are used to signify chloro, bromo, iodo and fluoro; the term acyl includes $R_{16}CO$ wherein R_{16} is H or alkyl of 1 to 5 carbons such as methanoyl and ethanoyl; the term aryl includes phenyl, alkylphenyl and naphthyl; the term N-monoalkylamidoalkyl includes $-CH_2CH_2CONHCH_3$,$-CH_2CONHCH_2CH_3$; the term N,N-dialkylamidoalkyl includes-$CH_2CON(CH_3)_2$; $CH_2CH_2CON(CH_2-CH_3)_2$. Compounds which are based on tellurium are the presently preferred compounds of the invention. The tellurium based compounds that are preferred include those of the formula:

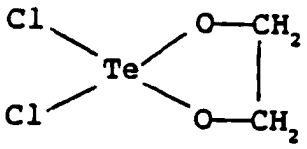


and

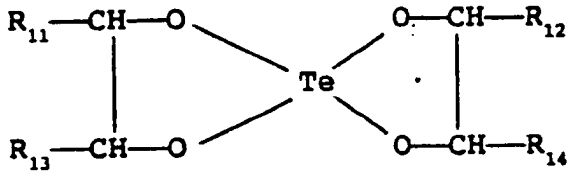


wherein X is halogen. The preferred halogen species is chloro.

Other compounds which are based on tellurium and may be used in the practice of the invention include $PhTeCl_3$, TeO_2 and TeX_4 $(C_{6H5})_4$ P + $(TeCl_3(O_2C_2H_4))$- (Z. Naturforsh, 36, 307-312 (1981). Compounds of the following structure are also included:



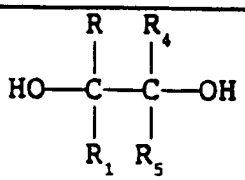
Other compounds useful for the practice of invention include:



wherein R_{11}, R_{12}, R_{13} and R_{14} are independently selected from the group consisting of hydrogen, hydroxyalkyl of 1-5 carbons atoms, hydroxy and alkyl of 1-5 carbons atoms.

Useful dihydroxy compounds for use in the preparation of compounds of structure A or B, include those of formula I wherein R, R_1, R_4 and R_5 are as shown in the Table:

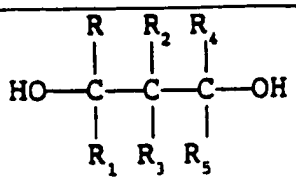
TABLE



(I)

R	R_1	R_4	R_5
H	H	H	H
H	Cl	H	H
H	OCH_3	H	H
H	$COOCH_3$	H	H
H	H	CN	H
H	CHO	H	H
H	H	COOH	H
H	CH_2COOH	H	H
H	H	CH_2COOCH_3	H
H	I	H	H
H	H	Br	H
H	H	$CONH_2$	H
H	H	CH_2OH	H
H	COOH	H	H

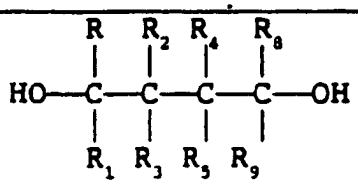
Other dihydroxy compounds for use in the preparation of compounds A and B include those of formula II wherein R, R_1, R_2, R_3, R_4 and R_5 are as shown in the Table:



(II)

R	R_1	R_2	R_3	R_4	R_5
H	H	H	H	H	H
H	H	Cl	H	H	H
H	CH_2OH	H	H	H	H
H	H	OH	H	H	H
H	H	H	CH_3	H	H
H	H	H	CH_2Cl	H	H
H	H	H	COOH	H	H
H	H	H	CH_2COOH	H	H
H	H	H	CHO	H	H
H	H	H	H	H	CH_2CHO
H	H	$CONH_2$	H	H	CH_3
H	H	H	CN	H	H
H	H	H	H	CH_2COHN_2	H
H	H	H	$COOCH_3$	H	H
H	H	OCH_3	H	H	H

Other dihydroxy compounds for use in making compound of formula A and B include those of formula III wherein R, R_1, R_2, R_3, R_4 and R_5 are as shown in the Table.

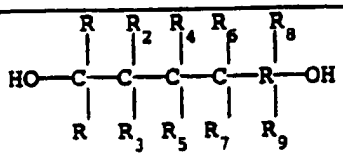


(III)

R	R_1	R_2	R_3	R_4	R_5	R_8	R_9
H	H	H	H	H	H	H	H
H	H	Cl	H	H	H	H	H
H	H	H	H	Br	H	H	H
H	H	OCH_3	H	H	H	H	H
H	H	$CONH_2$	H	H	H	H	H
H	Br	H	H	H	H	H	H
H	H	H	H	CH_2COOH	H	H	H
H	H	Cl	Cl	H	H	H	H
H	CH_2COOH	H	H	H	H	H	H
H	H	CH_3	H	H	H	H	H
H	CH_3	H	H	H	H	H	H
H	CH_2Cl	H	H	H	H	H	H
H	H	H	I	H	H	H	H
H	CH_2CN	H	H	H	H	H	H
H	H	H	H	CH_2CH_2OH	H	H	H

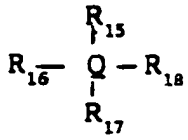
Additional dihydroxy compounds include those of formula IV wherein R, R_1, R_2, R_3, R_4 and R_5 are as shown in the Table.

(IV)



R	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9
H	H	H	H	H	H	H	H	H	H
H	H	Cl	H	H	H	Cl	H	H	H
H	H	Cl	Cl	H	H	H	H	H	H
H	H	$CONCH_3$	H	H	H	Br	H	H	H
H	H	Br	H	H	H	$CON(CH_3)_2$	H	H	H
H	H	H	OCH_3	H	H	H	H	H	H
H	H	H	H	OCH_3	H	H	H	H	H
H	H	H	H	CH_2COOH	H	H	H	H	H
H	H	COOH	H	H	H	H	H	H	H
H	CH_3	H	H	H	H	H	H	H	H
CH_3	H	H	H	H	CH_3	H	H	H	H
H	CH_2CH_3	H	H	H	H	H	Cl	H	H
H	CH_2CN	H	H	CH_2OH	H	H	H	H	H
H	H	H	I	H	H	H	H	CN	H
H	CH_2CH_2COOH	H	H	H	H	H	H	H	H
H	H	CHO	H	H	H	H	H	H	H
H	H	H	F	H	H	H	H	H	H

Compounds of the following formula are also included:



wherein R_{15}, R_{16}, R_{17} and R_{18} are independently selected from halogen, alkyl of 1-5 carbon atoms; aryl, acyl of 1-5 carbon hydroxyalkyl of 1-5 carbon atoms and aminoalkyl of 1-5 carbons may be made by reading the appropriate di, tri or tetrahaloselenide or telluride with the appropriate hydroxy compound which may be of the formula: HO-R_{19}; wherein R_{19}; is alkyl of 1 to 5 carbon atoms, haloalkyl of 1 to 5 carbon atoms, aryl, alkylaryl, alkylamido of 1 to 5 carbon atoms, alkylcarbonyl of 1 to 5 carbons, cyanoalkyl of 1 to 5 carbon atoms, cyanoalkyl of 1 to 5 carbon atoms, and an alkoxyalkyl of 2 to 10 carbon atoms. Specific examples of R_{16} include methyl, ethyl, n-propyl, phenyl, tolyl, amidoethyl, cyanomethyl, methyloxymethyl and CH_2CH_2COOH.

These compounds are described in US-A-4,761,490. In addition, $TeCl_4$; $TeBr_4$ and compounds which give in aqueous solution TeO_2 preferably in the form of a complex such as for example TeO_2 complex with citric acid or ethylene glycol.

The antineoplastic agents include alkylating agents such as nitrogen mustard, cyclophosphamide, melphan, and chlorambucil. The antimetabolites include purine antagonists such as 6-mercaptopurine and 6-thioguanine; pyrimidine antagonist are cytarabine, 5-fluorouracil, 5-floxuridine, and methotrexate. Plant alkaloids include vincristine, vinblastine, colchicine, etoposide and teniposide. Anti tumor antibiotics include dactinomycin, doxorubicin, daunomycin and mitomycin.

The tellurium compound may be administered by systemic administration by the intramuscular, intravenous

second day.

The invention also includes the treatment or invention of alopecia by the topical administration of effective amount of a tellurium compound onto to an area of the body where it is desired to cause hair to grow or to prevent the loss of hair. This aspect of the invention is applicable to the prevention of hair loss and is based on the application of an effective amount of a tellurium compound to areas of the body, such as the scalp or other areas where hair loss has been noticed.

Generally, any non-toxic vehicle may be used as a carrier for the tellurium compound at an effective concentration which will induce hair growth and/or retard and/or prevent hair loss.

Examples of suitable vehicles include petrolatum, Aquaphor, Neobase, propylene glycol and glycerin. These base materials are described in Remington's Pharmaceutical Sciences 17th Ed. Mack Publishing (1985), pp. 1301-1306. Generally, from 1 mg to 2.5 mg/Kg of body weight is applied once daily to the area to be treated. A preferred method of application is based on the use of a vehicle which is a thick liquid having a concentration of 200 µg of tellurium compound/0.2ml of solution.

When the method of the invention is practiced by parental administration, it may be preferred to administer the tellurium compound by subcutaneous injection at multiple sites (e.g. one injection per sq cm) within the affected area. The doses will be 0.25 mg/Kg to 2.5 mg/Kg of body weight given once daily, or in divided doses in an appropriate vehicle such as PBS. If desired, a dose regimen based on alternate day therapy may be used.

The tellurium compound should be administered prior to the administration of any neoplastic agent for optimal results in preventing alopecia induced by an antineoplastic compound. Simultaneous or subsequent administration of the tellurium compound with the antineoplastic agent may also be utilized.

The tellurium compound may be administered orally at 2.5 mg/Kg to 7.5 mg/Kg of body weight given once daily. If desired, a dose regimen based on alternate day therapy may be used.

EXAMPLE 1

The present invention is intended for use primarily in humans. In order to demonstrate the efficacy of the method of the invention, an animal model was chosen to carry out a controlled study to demonstrate the efficacy of the invention according to the method of Hussein et al., Science, Vol. 249, 28 Sept. 1990, pp. 1564-1566.

Sprauge Dawley rats, 8 days old were supplied by the Animal Supply Center of Bar-Ilan University, Israel. Arabinoside (ARC-C) was obtained from the Upjohn Company; cyclophosphamide (CTX) was obtained from Sigma; adriamycin (ADX) was obtained from Farmitalia and ammonium-trichloro (O,O'-dioxoethylene) tellurate was synthesized by the Department of Chemistry, Bar-Ilan University.

Arabinoside was injected intraperitoneally at a dose of 25 or 50 mg/kg day alone or with ammonium-trichloro (O,O'dioxoethylene)tellurate, dissolved in PBS, daily or every other day 2 hours prior to the administration of arabinoside. The cycle of treatment lasted 7 days. On day 9, the results were observed and graded according to the following protocol:

No detectable alopecia	0
Mild alopecia (hair loss <50%)	1+
Moderately severe alopecia (hair loss >50%)	2+
Total or virtually total alopecia (hair loss >79%)	3+

The observed results were as follows:

Treatment	No. of Subjects	Alopecia			
		0	1+	2+	3+
(a) arabinoside-C 25 mg/kg daily (x7days)	3	0	0	0	3
(b) arabinoside-C 25 mg/kg/i.p. ammonium trichloro (O,O'-dioxoethylene) tellurate 0.5 mg/Kg/IP (daily) (x7 days)	4	0	4	0	0
(c) arabinoside-C 25 mg/kg/i.p. ammonium trichlolo (O,O'-dioxoethylene) tellurate 0.5 mg/Kg/IP (every other day x 7 days)	4	0	4	0	0
(d) arabinoside-C 50 mg/kg/i.p. (x 7 days)	4	0	0	0	4
(e) arabinoside-C 50 mg/kg/i.p. ammonium trichloro (O,O'-dioxoethylene) tellurate 0.5 mg/Kg/IP (daily x 7 days)	4	0	3	1	0
(f) arabinoside-C 50 mg/kg/i.p. ammonium trichloro (O,O'-dioxoethylene) tellurate 0.5 mg/Kg/IP (every other day x 7 days)	4	0	1	3	0

A second experiment was carried out using the same procedure which is outlined above. The results were as follows:

Treatment	No. of Subjects	Alopecia			
		0	1+	2+	3+
(g) arabinoside-C 25 mg/kg/i.p. (x 7 days)	8	-	-	-	8
(h) arabinoside-C 25 mg/kg/i.p. (x 7 days) ammonium trichloro (O,O'-dioxoethylene) tellurate 0.5 mg/Kg/IP (daily) (x7 days)	6	6	-	-	-
(i) arabinoside-C 25 mg/kg/i.p. ammonium trichloro (O,O'-dioxoethylene) tellurate 0.5 mg/Kg/IP (every other day x 7 days)	6	6	-	-	-
(j) arabinoside-C 50 mg/kg/i.p. (x 7 days)	8	-	-	-	8
(k) arabinoside-C 50 mg/kg/i.p. x 7 days ammonium trichloro (O,O'-dioxoethylene) tellurate 0.5 mg/Kg/IP (daily x 7 days)	6	6	-	-	-
(l) arabinoside-C 50 mg/kg/i.p. ammonium trichloro (O,O'-dioxoethylene) tellurate 0.5 mg/Kg/IP (every other day x 7 days)	6	-	1	2	3

The results of these experiments shows that the addition of ammonium trichloro (O,O'-dioxoethylene)-tellurate to a treatment regimen which is based on arabinoside-C almost completely avoids alopecia when given daily and provides some protection from alopecia when given every other day. A histological examination of the skin of arabinoside-C treated subjects shows almost complete loss of hair follicles while the subjects who are treated with arabinoside-C and ammonium trichloro (O,O'-dioxoethylene) tellurate showed no hair loss or reduced hair loss.

EXAMPLE 2

An experiment was carried out to determine the effect of ammonium trichloro(O,O'-dioxoethylene)-tellurate on preventing the alopecia which is induced by cyclophosphamide using the procedure of Example 1.

The results are as follows:

Treatment	No. of Subjects	Alopecia			
		0	1+	2+	3+
(a) cyclophosphamide 20 mg/kg/i.p. (x 7 days)	8	-	2	3	5
(b) cyclophosphamide 20 mg/kg/i.p. ammonium trichloro (O,O' - dioxoethylene) tellurate 0.5 mg/Kg/IP (daily for 7 days)	8	0	4	0	0
(c) cyclophosphamide 20 mg/kg/i.p. (x 7 days)	10	-	3	5	2
(d) cyclophosphamide 20 mg/kg/i.p. (x 7 days) ammonium trichloro (O,O'-dioxoethylene) tellurate 0.5 mg/Kg/IP (daily x 7 days)	10	-	4	5	1
(e) cyclophosphamide 20 mg/kg/i.p. x 7 days	5	1	3	1	-
(f) cyclophosphamide 20 mg/kg/i.p. x 7 days ammonium trichloro (O,O'-dioxoethylene) tellurate 0.5 mg/Kg/IP daily x 7 days	5	2	2	1	-
(g) cyclosphosphamide 20 mg/Kg/i.p. x 7 days	10	-	10	-	-
(h) cyclophosphamide 20 mg/Kg/i.p. x 7 days ammonium trichloro (O,O'-dioxoethylene) tellurate 0.5 mg/Kg/IP (daily x 7 days)	10	6	4	-	-

This study shows that ammonium trichloro (O,O'-dioxoethylene)tellurate, at a level of 0.5 mg/kg/i.p., in conjunction with cyclophosphamide provides a mild protection against cyclophosphamide induced alopecia.

EXAMPLE 3

A number of Sprague Dawley rats were subjected to treatment with arabinoside C 25 mg/kg with ammonium trichloro (O,O'-dioxoethylene)tellurate by subcutaneous injection. The control compound was PBS. The results were as follows:

	Exp. 1	Exp. 2	Exp. 3
ammonium trichloro (O,O'-dioxoethylene)tellurate 0.25 mg/Kg/s.c daily x 7 days	3/4	5/7	7/10
PBS	0/3	0/6	ND*

* ND = not done

EXAMPLE 4

A stock composition of 1 mg. of ammonium trichloro (O,O'-dioxoethylene) tellurate in 1 ml. of glycerin was prepared. The stock composition was diluted with glycerin to give the following concentrations per ml. so that the stated dose could be applied topically by application of 1 ml. of solution. The solution was applied to the entire back surface of rats once daily for a period of 7 days. Two hours after each treatment the rats were injected with 25 mg/kg of arabinoside-C once daily. Control rats were treated with a glycerin and injected with arabinoside-C. The following results were observed:

Concentration of Ammonium trichloro (O,O'-dioxoethylene) tellurate (ug/rat)	Grade of Alopecia*	No. of rats in Group
200	3	5
100	2	5
50	0	5
20	1	5
10	3	5
0	4	5

*0 = no alopecia; 1 = less than 20% alopecia; 2 = less than 50% alopecia; 3 = more than 50% alopecia; 4 = total alopecia.

A dose response effect was observed which is attributed to the ammonium trichloro (O,O'-dioxoethylene) tellurate. All control animals that were treated with arabinoside C ...

whereas 100% of the rats treated with 50 ug of ammonium trichloro (O,O'-dioxoethylene) tellurate showed 0% alopecia.

EXAMPLE 5

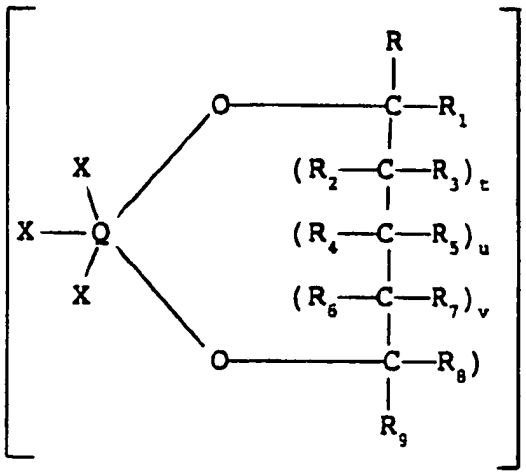
A phase II chemotherapy trial was carried out in patients having unresectable and metastatic non-small cell lung tumors. The chemotherapy was based on carboplatinum 300.0 mg/m^2/IV daily and etoposide 200.0 mg/m^2 on day 3, 5 and 7 for a total of 12 weeks of chemotherapy which was given to group I. In addition to the same chemotherapy, ammonium trichloro (O,O'-dioxoethylene)tellurate was given to Group II at a dose of 3 mg/m^2 three times a week starting two weeks before the chemotherapy and continued for 12 weeks after the chemotherapy. The alopecia of both groups was observed 12 weeks after the chemotherapy and was as follows:

ALOPECIA SCORE						
	0	I	II	III	IV	Total
Group I	68 45.64%	22 14.77%	29 19.46%	28 18.79%	2 1.35%	149
Group II	122 61.00%	26 13.00%	40 20.00%	12 6.00%	0 0.00%	200

0 - no alopecia
I - casual alopecia
II - >50% alopecia
III - <50% alopecia
IV - total alopecia

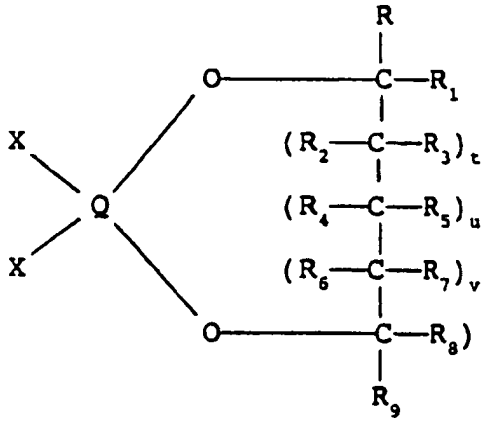
Claims

1. Use, for the manufacture of a medicament to be employed in the prevention or treatment of alopecia, of a compound, which is:



(A)

or



(B)

or

TeO_2 or complexes of TeO_2 (C)

or

$PhTeCl_3$ (D)

or

$(C_6H_5)_4\ P^+(TeCl_3(O_2C_2H_4))^-$ (E)

or

TeX_4, (F)

wherein Q is Te or Se; t is 1 or 0; u is 1 or 0; v is 1 or 0; R, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are the same or different and are independently selected from hydrogen, hydroxyalkyl of 1 to 5 carbon atoms, hydroxy, alkyl of 1 to 5 carbon atoms, halogen, haloalkyl of 1 to 5 carbon atoms, carboxy, alkylcarbonylalkyl of 2 to 10 carbon atoms, alkanoyloxy of 1 to 5 carbon atoms, carboxyalkyl of 1 to 5 carbons atoms, acyl, amido, cyano, amidoalkyl of 1 to 5 carbon atoms, N-monoalkylamidoalkyl of 2 to 10 carbon atoms, N,N-dialkylamidoalkyl of 4 to 10 carbon atoms, cyanoalkyl of 1 to 5 carbon atoms

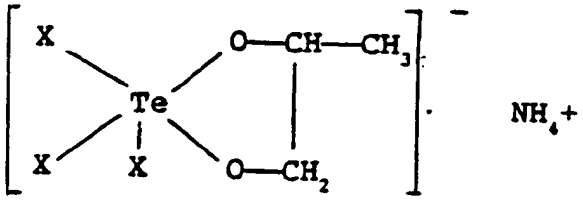
from 1 to 5 carbon atoms; Y is a cation and X is halogen;
or pharmaceutically acceptable salts and complexes thereof.

2. Use as defined in claim 1, wherein Y is ammonium.

3. Use as defined in claim 1, wherein the pharmaceutically acceptable salts are ammonium or potassium.

4. Use as defined in claim 1, wherein the compound is ammonium trichloro (O,O'-dioxoethylene tellurate).

5. Use as defined in claim 1, wherein the compound is



wherein X is chloro.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 93 20 2226

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,Y	US-A-4 761 490 (ALBECK ET AL.) 2 August 1988 * see the claims, column 7 line 8 - column 8 line 26, examples 7-21*	1-5	A61K31/33 A61K31/66 A61K33/04
Y	CHEMICAL ABSTRACTS, vol. 108, 1988, Columbus, Ohio, US; abstract no. 73477u, page 519 ; * abstract * & ZHONGGUO MIANYIXUE ZAZHI vol. 3, no. 4, 1987, pages 223 - 226 GUO H. 'Defective production of interleukin-2 (IL-2) in patients with alopecia areata'	1-5	
A	FASEB J. vol. 5, 1991, pages 2456 - 2458 JIMENEZ JJ. ET AL. 'Interleukin 1 protects from cytosine arabinoside-induced alopecia in the rat model' * see the discussion *	1	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	21 OCTOBER 1993	B. ISERT

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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